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(54) Title: AMIDE DERIVATIVES AS 5HT1D RECEPTOR ANTAGONISTS

(57) Abstract

Novel amide derivatives, processes for their preparation, and pharmaceutical compositions containing them.

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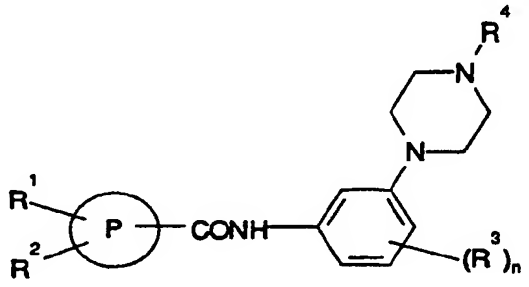
AMIDE DERIVATIVES AS 5HT1D RECEPTOR ANTAGONISTS

The present invention relates to novel amide derivatives, processes for their preparation, and pharmaceutical compositions containing them.

EPA 0 533 266/7/8 disclose a series of benzanilide derivatives which are said to possess $5HT_{1D}$ receptor antagonist activity. These compounds are alleged to be of use in the treatment of various CNS disorders.

A structurally distinct class of compounds have now been discovered and have been found to exhibit $5HT_{1D}$ antagonist activity. In a first aspect, the present invention therefore provides a compound of formula (I) or a salt thereof:



(I)

in which

P is a phenyl or a 5 or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, nitrogen or sulphur;

R^1 is halogen, C_{1-6}alkyl, C_{1-6}cycloalkyl, optionally substituted phenyl or an optionally substituted 5-7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, trifluoromethyl or cyano;

R^3 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

R^4 is hydrogen or C_{1-6}alkyl; and

n is 1 or 2,

- provided that when P is phenyl R^1 is not pyridyl or phenyl.

C_{1-6}alkyl groups, whether alone or as part of another group, may be straight chain or branched.

Suitably P is a phenyl or a 5 or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, nitrogen or sulphur. Examples of rings P include pyridyl, thienyl, furyl and pyrrolyl rings. Preferably P is phenyl, thienyl, furyl or pyridyl.

Suitably R^1 is halogen, C_{1-6}alkyl, C_{1-6}cycloalkyl, optionally substituted phenyl or an optionally substituted 5-7-membered heterocyclic ring containing 1 to 3 heteroatoms

selected from oxygen, nitrogen or sulphur. The group R^1 can be an aromatic or saturated heterocyclic ring. When R^1 is an aromatic heterocyclic ring, examples of such rings include pyridyl, thienyl, furyl, pyrrolyl, oxadiazolyl, pyrazolyl, triazolyl, diazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrimidyl and pyrazinyl. When R^1 is a saturated ring examples include piperidine, morpholine and piperazine rings. Optional substituents for R^1 include halogen, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, cyano, nitro, amino, CO_2R^5 where R^5 is hydrogen or C_{1-6}alkyl or $CONR^6R^7$ where R^6 and R^7 are independently hydrogen or C_{1-6}alkyl.

Preferably R^1 is halogen, butyl, cyclohexyl, pyridyl, pyrazolyl, triazolyl, imidazolyl, morpholinyl, piperazinyl or thienyl.

Suitably R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy or nitro. Preferably R^2 is hydrogen, C_{1-6}alkoxy, for example methoxy, C_{1-6}alkyl, for example methyl, or nitro.

Suitably R^3 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy. Preferably R^3 is C_{1-6}alkoxy such as methoxy.

Preferably n is 1 and the group R^3 is para to the amide linkage.

Suitably R^4 is hydrogen or C_{1-6}alkyl. Preferably R^4 is C_{1-6}alkyl such as methyl.

Particularly preferred compounds include:

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(4-pyridyl)furan-2-carboxamide,
N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(4-pyridyl)furan-3-carboxamide,
N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(4-pyridyl)thiophene-2-carboxamide,
N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-(4-pyridyl)pyridine-5-carboxamide,
N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-(4-pyridyl)-3-methoxythiophene-4-carboxamide,
N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(2-pyridyl)thiophene-2-carboxamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(1,2,4-triazol-1-yl) benzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(imidazol-1-yl) benzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(morpholin-1-yl) benzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(3-thiophenyl)-3-methylbenzamide,
N-(4-methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(1,2,4-triazol-1-yl)-3-nitrobenzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-3-nitro-4-pyrazolylbenzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(4-ethoxycarbonylpiperazin-1-yl)benzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-fluorobenzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-chlorobenzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-iodobenzamide,

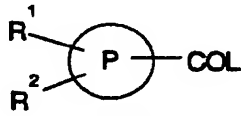
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-cyclohexylbenzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-tert-butylbenzamide,
or a pharmaceutically acceptable salt thereof.

Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

Certain compounds of formula (I) are capable of existing in steroisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates. Tautomers of compounds of formula (I) and mixtures thereof also form an aspect of the invention.

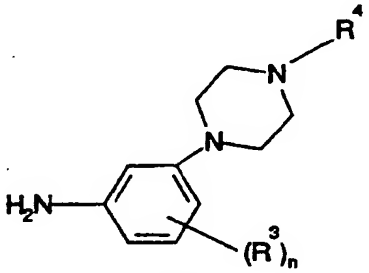
In a further aspect the present invention provides a process for the preparation of a compound of formula (I) which comprises.

(a) reaction of a compound of formula (II):



(II)

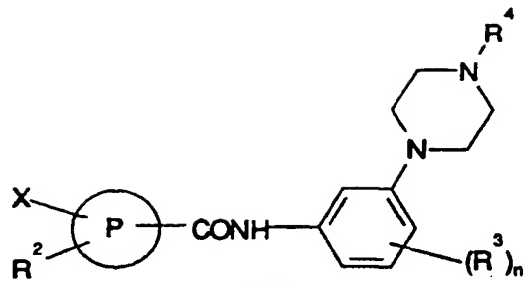
in which R^1, R^2 and P are as defined in formula (I) and L is a leaving group, with a compound of formula (III):



(III)

in which R^3, R^4 and n are as defined in formula (I);

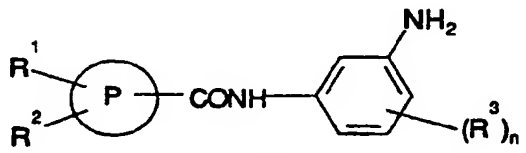
(b) for compounds of formula (I) in which R^1 is a phenyl or heterocyclic ring reaction of a compound of formula (IV):



(IV)

in which R^2, R^3, R^4, P and n are as defined in formula (I) and X is a leaving group with a nucleophile R^1 where R^1 is as defined in formula (I); or

(c) reaction of a compound of formula (V):



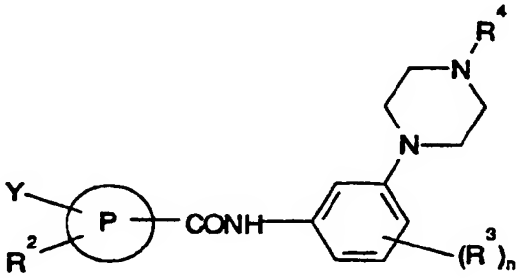
(V)

in which R^1, R^2, R^3, P and n are as defined in formula (I) with a compound of formula (VI):

$$R^4N(CH_2CH_2Hal)_2 \qquad (VI)$$

in which R^4 is as defined in formula (I) and Hal is halogen, or

(d) reaction of a compound of formula (VII):



(VII)

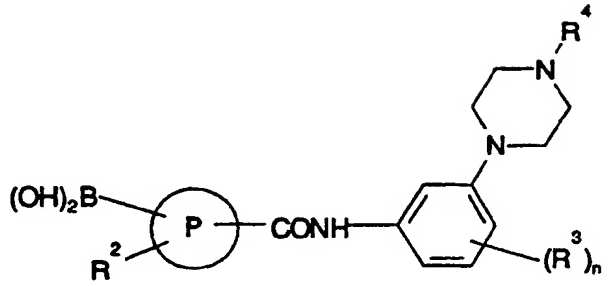
in which R^2, R^3, R^4, P and n are as defined in formula (I) and Y is halogen or a group $-OSO_2CF_3$ with a compound of formula (VIII):

$R^1B(OH)_2$

(VIII)

in which R^1 is as defined in formula (I), or

(e) reaction of a compound of formula (IX):



(IX)

in which R^2, R^3, R^4, P and n are as defined in formula (I) with a compound of formula (X):

R^1Y

(X)

in which R^1 is as defined in formula (I) and Y is as defined in formula (VII),

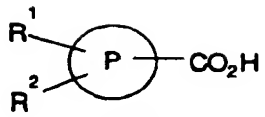
and optionally thereafter:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

Suitable activated carboxylic acid derivatives of formula (II) include acyl halides and acid anhydrides. Activated compounds of formula (II) can also be prepared by reaction of the corresponding carboxylic acid with a coupling reagent such as carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphorylazole. Preferably the group L is halo, particularly chloro.

A compound of formula (II) is typically reacted with a compound of formula (III) in an inert organic solvent such as DMF, THF or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

Compounds of formula (II) can be prepared from a compound of formula (XI):



(XI)

in which R^1, R^2 and P are as defined in formula (I) using standard procedures. For example acid chlorides can be prepared by reaction with phosphorous pentachloride, oxalyl chloride or thionyl chloride. Acid anhydrides can be prepared by reaction with a suitable acid anhydride, for example trifluoroacetic anhydride.

Reaction of a compound of formula (IV) with a nuclephile R^1 is preferably carried out in a suitable solvent such as dimethylformamide in the presence of a strong base such as sodium hydride. Preferably the leaving group X is halo, in particular fluoro. Preferably the group R^2 is an electron withdrawing group, for example nitro, $COCH_3$ or cyano, in the ortho or para-positions relative to the group X.

Reaction of a compound of formula (V) with a compound of formula (VI) is suitably carried out in an alcohol or nitrile solvent with an optional base or, alternatively, in a non-polar solvent such as chlorobenzene in the absence of base. Suitably, the reactions are carried out at ambient or elevated temperature, preferably at the reflux temperature of the reaction mixture.

Reaction of compounds of formula (VII) and (VIII) and reaction of compounds of formulae (IX) and (X) can be carried out in the presence of a transition metal catalyst such as $Pd(PPh_3)_4$ in a solvent such as an ether in the presence of a base such as an alkali metal carbonate or bicarbonate, for example sodium carbonate or bicarbonate, at ambient or elevated temperature.

Certain compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures. For example R^2/R^3 halogens can be introduced by halogenation.

Intermediate compounds of formulae (III), (IV), (V), (VI), (VII), (VIII), (IX), (X) and (XI) are commercially available or can be prepared using standard procedures such as those outlined in EPA 533266/7/8.

Certain compounds of formulae (IV), (V), (VII) and (IX) are novel and form a further aspect of the invention.

It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures, for example when the group R^4 is a hydrogen atom. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional procedures.

Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

$5HT_{1D}$ Antagonists, and in particular the compounds of the present invention, are expected to be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal effective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnestic disorders and age-associated memory impairment; and disorders of eating behaviours, including anorexia nervosa and bulimia nervosa. Other CNS disorders include Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

$5HT_{1D}$ Antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, in the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointenstinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction.

Therefore, the present invention, provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy.

The present invention also provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

In another aspect the invention provdes the use of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of the aforementioned disorders.

In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In particular the invention provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to

1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention.

Description 1
2-Bromo-5-pyridinecarboxylic acid

2,5-dibromopyridine (1.0g;4.22mmol) was cooled to -78°C in dry Et_2O (10ml) under Ar and treated with ^nBuLi (2.64ml;4.22mmol of a 1.6M solution in hexanes) rapidly, stirred for 5 minutes and treated with solid CO_2. Allowed to warm to RT, treated with H_2O (10ml) and the aqueous layer separated then washed with Et_2O. The aqueous phase was acidified with conc.HCl(aq) and the precipitate that formed was collected by filtration and dried *in vacuo* to yield the title compound as a pale yellow solid (0.35g;41%).

^{1} NMR (250MHz, $CDCl_3$) δ : 8.90(d,1H), 8.20(d,1H), 7.65(d,1H)

Description 2
5-Bromo-2-thiophenecarboxylic acid

5-Bromo-2-thiophenecarboxaldehyde (1.0g;5.24mmol) was dissolved in acetone (4ml) and treated with 20%Na_2CO_3(aq) (0.53ml). $KMnO_4$ (0.827;5.24mmol) was added portionwise and the solution stirred for 1 hour at RT. The reaction mixture was filtered through kieselguhr and the filtrate treated with H_2O_2 (0.8ml of a 27% solution in water). When all effervesence had ceased, the aqueous was acidified with conc.HCl(aq) and a yellow solid precipitated. The suspension was extracted with EtOAc, the extracts combined and dried over Na_2SO_4, filtered, and the filtrate evaporated *in vacuo* to a yellow liquid. The liquid was diluted with hexane and cooled to -78°C. The solid that formed was collected by filtration and dried to yield the title compound as a pale yellow solid (0.3g;28%).

^{1}H NMR (250MHz, $CDCl_3$) δ : 7.65(d,1H), 7.15(d,1H)

Description 3
5-Bromo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]furan-2-carboxamide

5-Bromofuroic acid (0.432;2.26mmol) was heated at reflux in thionyl chloride (10ml) for 30 minutes, cooled, evaporated *in vacuo* and the residue azeotroped with toluene. The residue was redissolved in CH_2Cl_2 (10ml) and treated with dry triethylamine (0.32ml;2.26mmol) and 4-methoxy-3-(4-methyl-1-piperazinyl)benzenamine (0.5g;2.26mmol). The solution was stirred under Ar (18 hours), evaporated *in vacuo* and partitioned satd. K_2CO_3(aq) / EtOAc. The organic phases were combined, dried over

Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to a brown gum. The gum was purified by flash silica-gel chromatography and eluted with 2%MeOH/$CHCl_3$ to yield the title compound as a pale yellow foam (0.77g;86%), which was converted to the oxalate salt, mp=125-127°C.

^1H NMR (250MHz, $CDCl_3$) (free base) δ : 7.90(s, 1H), 7.40-7.15(m,3H), 6.85(d,1H), 6.50(d,1H), 3.90(s,3H), 3.25-3.05(m,4H), 2.70-2.50(m,4H), 2.40(s,3H)

Description 4

5-Bromo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]furan-3-carboxamide

5-Bromo-3-furancarboxylic acid (0.302;1.58mmol) was heated at reflux in thionyl chloride (8ml) for 30 minutes, cooled, evaporated *in vacuo* and the residue azeotroped with toluene. The residue was redissolved in CH_2Cl_2 (10ml) and treated with dry triethylamine (0.22ml;1.58mmol) and 4-methoxy-3-(4-methyl-1-piperazinyl)benzenamine (0.35g;1.58mmol). The solution was stirred under Ar (18 hours), evaporated *in vacuo* and partitioned satd. K_2CO_3(aq) / EtOAc. The organic phases were combined, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to a brown gum. The gum was purified by flash silica-gel chromatography and eluted with 3%MeOH/$CHCl_3$ to yield the title compound as a tan solid after trituration with Et_2O (0.3g;48%), mp=185-187°C.

^1H NMR (250MHz, $CDCl_3$) (free base) δ : 8.85(s,1H), 8.20(s,1H), 7.40(d,1H), 7.15(s,1H), 7.40(s,1H), 6.70(d,1H), 3.80(s,3H), 3.20-2.90(m,4H), 2.80-2.60(m,4H), 2.40(s,3H)

Description 5

5-Bromo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]thiophene-2-carboxamide

5-Bromo-2-thiophenecarboxylic acid (0.375;1.81mmol) was heated at reflux in thionyl chloride (8ml) for 30 minutes, cooled, evaporated *in vacuo* and the residue azeotroped with toluene. The residue was redissolved in CH_2Cl_2 (10ml) and treated with dry triethylamine (0.25ml;1.81mmol) and 4-methoxy-3-(4-methyl-1-piperazinyl)benzenamine (0.4g;1.81mmol). The solution was stirred under Ar (18 hours), evaporated *in vacuo* and partitioned satd. K_2CO_3(aq) / EtOAc. The organic phases were combined, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to a brown gum. The gum was purified by flash silica-gel chromatography and eluted with 3%MeOH/$CHCl_3$ to yield the

title compound as a brown gum which crystallised on standing (0.388g;52%), and was converted to the oxalate salt, mp=114-115°C.

^{1}H NMR (250MHz, $CDCl_3$) (free base) δ : 8.60(s,1H), 7.70(d,1H), 7.50(d,1H), 7.20(s,1H), 7.10(d,1H), 6.80(d,1H), 3.80(s,3H), 3.30-2.75(m,8H), 2.55(s,3H)

Description 6
2-Bromo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]pyridine-5-carboxamide

2-Bromo-5-pyridinecarboxylic acid (0.34g;1.68mmol) was heated at reflux in thionyl chloride (8ml) for 1 hour, cooled, evaporated *in vacuo* and the residue azeotroped with toluene. The orange residue was redissolved in CH_2Cl_2 (6ml) and treated with dry triethylamine (0.24ml;1.68mmol) and 4-methoxy-3-(4-methyl-1-piperazinyl)benzenamine (0.372g;1.68mmol). The solution was stirred under Ar (18 hours), evaporated *in vacuo* and partitioned satd. K_2CO_3(aq) / EtOAc. The organic phases were combined, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to a brown gum. The gum was purified by flash silica-gel chromatography and eluted with 3%MeOH/$CHCl_3$ to yield the title compound as brown crystals after trituration with acetone / Et_2O (0.13g;19%).

^{1}H NMR (200MHz, $CDCl_3$) δ : 9.90(s,1H), 9.00(d,1H), 8.30(d,1H), 7.50-7.30(m,3H), 6.80(d,1H), 3.85(s,3H), 3.30-3.00(m,4H), 2.80-2.65(m,4H), 2.40(s,3H)

Description 7
2-Bromo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-3-methoxythiophene-4-carboxamide

2-Bromo-3-methoxythiophene-4-carboxylic acid (0.429g;1.81mmol) was heated at reflux in thionyl chloride (8ml) for 1 hour, cooled, evaporated *in vacuo* and the residue azeotroped with toluene. The orange residue was redissolved in CH_2Cl_2 (5ml) and treated with dry triethylamine (0.25ml;1.81mmol) and 4-methoxy-3-(4-methyl-1-piperazinyl)benzenamine (0.4g;1.81mmol). The solution was stirred under Ar (18 hours), evaporated *in vacuo* and partitioned satd. K_2CO_3(aq) / EtOAc. The organic phases were combined, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to a brown gum. The gum was purified by flash silica-gel chromatography and eluted with 2%MeOH/$CHCl_3$ to yield the title compound as white powder after trituration with Et_2O (0.43g;54%), mp=120-122°C.

^{1}H NMR (250MHz, $CDCl_3$) δ : 9.10(s,1H), 8.10(s,1H), 7.30(d,1H), 7.20(d,1H), 6.80(d,1H), 4.10(s,3H), 3.90(s,3H), 3.25-3.10(m,4H), 2.75-2.60(m,4H), 2.40(s,3H)

Description 8
Ethyl 4-(1,2,4-triazol-1-yl)benzoate

1,2,4-Triazole (0.82g, 0.01mol), ethyl 4-fluorobenzoate (2g, 0.01mol) and anhydrous potassium carbonate (1.43g, 0.011mol) was dissolved in DMSO (30ml) and heated to 90°C for 18h. The solution was poured into water (50ml), extracted with ethyl acetate (50ml), dried (sodium sulphate), filtered and evaporated to dryness under reduced pressure. the white solid was purified by flash column chromatography (silica, diethyl ether) to afford a white solid (1.59g, 73%).

1H NMR ($CDCl_3$) δ 1.43 (3H, t), 4.42 (2H, q), 7.81 (2H, d), 8.15 (1H, s), 8.21 (2H, d), 8.68 (1H, s).

Description 9
Ethyl 4-(imidazol-1-yl)benzoate

Imidazole (0.816g, 0.011mol), ethyl 4-fluorobenzoate (2g, 0.01mol) and anhydrous potassium carbonate (1.43g, 0.011mol) was dissolved in DMSO (30ml) and heated to 90°C for 18h. The solution was poured into water (50ml), extracted with ethyl acetate (50ml), dried (sodium sulphate), filtered and evaporated to dryness under reduced pressure. the white solid was purified by flash column chromatography (silica, diethyl ether) to afford a white solid (1.22g, 56%).

1H NMR ($CDCl_3$) δ: 1.43 (3H, t), 4.42 (2H, q), 7.28 (1H, s), 7.38 (1H, s), 7.48 (2H, d), 7.95 (1H, s), 8.19 (2H, d).

Description 10
Ethyl 4-(morpholin-1-yl)benzoate

Morpholine (1.04ml, 0.011mol), ethyl 4-fluorobenzoate (2g, 0.01mol) and anhydrous potassium carbonate (1.43g, 0.011mol) was dissolved in DMSO (30ml) and heated to 90°C for 18h. The solution was poured into water (50ml), extracted with ethyl acetate

(50ml), dried (sodium sulphate), filtered and evaporated to dryness under reduced pressure. the white solid was purified by flash column chromatography (silica, diethyl ether) to afford a white solid (1.39g, 59%).

1H NMR ($CDCl_3$) δ: 1.43 (3H, t), 3.24 (4H, q), 3.72 (4H, q), 4.42 (2H, q), 7.00 (2H, d), 7.78 (2H, d).

Description 11
Ethyl 4-(4-ethoxycarbonylpiperazin-1-yl)benzoate

Ethyl 4-fluorobenzoate (0.93ml, 6.3mmol), anhydrous potassium carbonate (0.96g, 7.0mmol), ethoxycarbonyl piperazine (0.92ml, 6.3mmol)and dry DMSO (30ml) were heated under dry conditions at 90°C for 72h. The mixture was partitioned between ethyl acetate and water, dried (sodium sulphate) and evaporated to dryness under reduced pressure. The product was purified by flash column chromatography on silica eluting with 10%MeOH/chloroform to afford the title compound as an oil (1.35g, 70%).

1H NMR ($CDCl_3$) 1.29 (3H, t), 1.38 (3H, t), 3.32 (4H, m), 3.64 (4H, m), 4.19 (2H, q), 4.33 (2H, q), 6.87 (2H, d), 7.95 (2H, d).

Example 1
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(1,2,4-triazol-1-yl) benzamide

Ethyl 4-(1,2,4-triazol-1-yl)benzoate (520mg, 2.4mmol) was heated at reflux in 5N HCl (40ml) for 1h, and the product filtered off and dried *in vacuo* to afford the acid (88%). 4-(1,2,4-triazol-1-yl)benzoic acid (0.395g, 2.1mmol) was suspended in dry toluene (40ml) and thionyl chloride (2ml) added under argon. The mixture was heated to reflux for 1.5h and then evaporated to dryness under reduced pressure.the oil was dissolved in dichloromethane under argon and 4-methoxy-3-(4-methyl-1-piperazinyl)phenylamine (460mg, 2.1mmol) was added followed by triethylamine (2ml). The mixture was stirred at room temperature under argon for 2h and then partitioned between dichloromethane (50ml) and saturated potassium carbonate (50ml), and the organic extracts dried (sodium sulphate). The organic solution was filtered, evaporated to dryness under reduced pressureand purified by column chromatography (silica, chloroform/methanol 5-10%) to afford the amide (757mg, 92%) which was crystallised from methanol diethyl ether as the oxalate salt.

1H NMR ($CDCl_3$) (free base) δ: 2.38 (3H, s), 2.65 (4H, bm), 3.13 (4H, bm), 3.89 (3H, s), 6.88 (1H, d), 7.22 (1H, s), 7.74 (1H, s), 7.84 (2H, d), 8.03 (2H, d), 8.18 (1H, s), 8.68 (1H, s).

Example 2

N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(imidazol-1-yl) benzamide

Ethyl 4-(imidazol-1-yl)benzoate (0.5g, 2.3 mmol) was heated at reflux in 5N HCl (40ml) for 1h, evaporated to dryness under reduced pressure and the resulting white solid dried *in vacuo* to afford 4-(imidazol-1-yl)benzoic acid. This was suspended in dry toluene (40ml) and thionyl chloride (2ml) added under argon. The mixture was heated to reflux for 1.5h and then evaporated to dryness under reduced pressure.the oil was dissolved in dichloromethane under argon and 4-methoxy-3-(4-methyl-1-piperazinyl)phenylamine (551mg, 2.3mmol) was added followed by triethylamine (2ml). The mixture was stirred at room temperature under argon for 2h and then partitioned between dichloromethane (50ml) and saturated potassium carbonate (50ml), and the organic extracts dried (sodium sulphate). The organic solution was filtered, evaporated to dryness under reduced pressureand purified by column chromatography (silica, chloroform/methanol 5-10%) to afford the amide (809mg, 90%) which was crystallised from methanol diethyl ether as the oxalate salt.

1H NMR ($CDCl_3$) (free base) δ: 2.38 (3H, s), 2.66 (4H, bm), 3.15 (4H, bm), 3.90 (3H, s), 6.87 (1H, d), 7.29 (2H, m), 7.37 (1H, s), 7.52 (2H, d), 7.86 (1H, s), 7.93 1H, s), 8.01 (2H, d).

Example 3

N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(morpholin-1-yl) benzamide

Ethyl 4-(morpholin-1-yl)benzoate (564mg, 2.4mmol) was heated at reflux in 5N HCl (40ml) for 1h, evaporated to dryness and dried in vacuo to afford 4-(morpholin-1-yl)benzoic acid. This was suspended in dry toluene (40ml) and thionyl chloride (2ml) added under argon. The mixture was heated to reflux for 1.5h and then evaporated to dryness under reduced pressure.the oil was dissolved in dichloromethane under argon and 4-methoxy-3-(4-methyl-1-piperazinyl)phenylamine (530mg, 2.4mmol) was added followed by triethylamine (2ml). The mixture was stirred at room temperature under argon for 2h and then partitioned between dichloromethane (50ml) and saturated potassium carbonate (50ml), and the organic extracts dried (sodium sulphate). The organic solution

was filtered, evaporated to dryness under reduced pressureand purified by column chromatography (silica, chloroform/methanol 5-10%) to afford the amide (925mg, 94%) which was crystallised from methanol diethyl ether as the oxalate salt.

1H NMR ($CDCl_3$) (free base) δ: 2.35 (3H, s), 2.62 (4H, bm), 3.14 (4H, bm), 3.28 (4H, m), 3.89 (7H, s and m), 6.83 (1H, d), 6.93 (2H, d), 7.22 (1H, s), 7.62 (1H, s), 7.80 (2H, d).

Example 4

N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(3-thiophenyl)-3-methylbenzamide

N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-bromo-3-methylbenzamide (0.35g, 0.84mmol), sodium carbonate (89mg, 0.84mmol), tetrakis (triphenylphosphine)palladium(0) (49mg, 0.05 equiv), 3-thiophenyl boronic acid (115mg, 0.84mmol) in water (18ml) and DME (18ml) were heated at reflux under argon for 18h. The solution was partitioned between saturated aqueous potassium carbonate solution (50ml) and chloroform (50ml), the organic extracts dried (sodium sulphate), filtered and evaporated to dryness under reduced pressure. The resulting oil was purified by column chromatography (silica, chloroform/methanol 5-30%) to afford the title compound as an oil (242mg, 63%) which was crystallised as an oxalate salt from methanol chloroform.

1H NMR (D6-DMSO) δ: 2.42 (3H, s), 2.82 (3H, s), 3.32 (8H, bm, 4xCH_2), 3.80 (3H, s), 6.98 (1H d), 7.32 (1H, d), 7.46 (3H, m), 7.68 (2H, m), 7.81 (1H, d), 7.90 (1H, d).
Mass Spectrum M^+ found 421, $C_{24}H_{27}N_3O_2S$ requires 421
Analysis Found C 53.26; H 5.03; N 6.63.
$C_{24}H_{27}N_3O_2S.2C_2H_2O_4.1.5H_2O$ requires C 53.50; H 5.41; N 6.69.

Example 5

N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(1,2,4-triazol-1-yl)-3-nitrobenzamide oxalate

4-(1,2,4-triazol-1-yl)-3-nitrobenzoic acid (100mg, 0.43 mmol) was suspended in dry toluene (40ml) and thionyl chloride (1ml) added under argon. The mixture was heated at reflux for 1.5h and the resulting yellow solution evaporated to dryness under reduced pressure. The oil was dissolved in dry dichloromethane (40ml) under argon and 4-methoxy-5-(4-methyl-1-piperazinyl)phenylamine (94mg, 0.43mmol) was added followed by triethylamine (0.06ml). The mixture was stirred for 2h under argon,

partitioned between dichloromethane and saturated aqueous potassium carbonate(50ml) and the organic extracts dried (sodium sulphate). The solution was evaporated to dryness under reduced pressure and purified by column chromatography (silica, chloroform/methanol 5-10%) to afford the amide (153mg,81%) as an oil which was crystallised from methanol/diethyl ether as the oxalate salt, m.p. 223 - 225°C.

1H NMR ($CDCl_3$) (free base) δ 2.68 (4H, bm), 3.10 (4H, bm), 3.51 (3H, s), 3.89 (3H, s), 6.83 (1H, d), 7.18 (1H, s), 7.38 (1H, dd), 7.69 (1H, d), 8.15 (1H, d), 8.31 (1H, dd), 8.53 (2H, d), 8.90 (1H, bs, NH).
Mass Spectrum M+ 437. $C_{21}H_{23}N_7O_4$ requires 437
Analysis C 52.44, H 5.11, N 18.87
$C_{21}H_{23}N_7O_4.C_2H_2O_4$ requires C 52.37, H 4.78, N 18.59.

Example 6

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(4-pyridyl)furan-2-carboxamide

5-bromo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]furan-2-carboxamide (0.3g;0.76mmol) was stirred with 4-pyridylboronic acid (0.094g;0.76mmol), tetrakis(triphenylphosphine)palladium(0) (0.045g;5 mol%) and anhydrous sodium carbonate (0.089g;0.84mmol) in water (14ml) and DME (14ml) and the whole heated at reflux under Ar (18 hours). The reaction mixture was poured into 10% Na_2CO_3(aq) (30ml) and extracted into $CHCl_3$. The organic extracts were combined, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to a brown oil which crystallised on standing. The brown solid was purified by flash silica-gel chromatography and eluted with 3%MeOH/$CHCl_3$ to yield the title compound as a lemon solid (0.22g;74%), mp=157-159°C.

^{1}H NMR (200MHz, $CDCl_3$) δ : 8.70(d,2H), 8.00(s,1H), 7.60(d,2H), 7.35-7.15(m,3H), 7.00(d,1H), 6.85(d,1H) 3.85(s,3H), 3.20-3.05(m,4H), 2.70-2.55(m,4H), 2.35(s,3H)

Example 7

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(4-pyridyl)furan-3-carboxamide

5-bromo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]furan-3-carboxamide (0.16g;0.41mmol) was stirred with 4-pyridylboronic acid (0.050g;0.41mmol), tetrakis(triphenylphosphine)palladium(0) (0.024g;5 mol%) and anhydrous sodium carbonate (0.047g;0.45mmol) in water (8ml) and DME (8ml) and the whole heated at

reflux under Ar (18 hours). The reaction mixture was poured into 10% Na_2CO_3(aq) (20ml) and extracted into $CHCl_3$. The organic extracts were combined, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to a brown gum. The gum was purified by flash silica-gel chromatography and eluted with 4%MeOH/$CHCl_3$ to yield a orange oil which was triturated with hexane/Et_2O. The solid that formed was collected by filtration and dried *in vacuo* to yield the title compound as a tan solid (0.029g;18%), mp=103-105°C.

^{1}H NMR (250MHz, $CDCl_3$) δ : 8.65(d,2H), 8.15(s,1H), 7.65(s,1H), 7.55(d,2H), 7.35-7.10(m,3H), 6.85(d,1H) 3.90(s,3H), 3.20(m,4H), 2.70-2.55(m,4H), 2.40(s,3H)

Example 8

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(4-pyridyl)thiophene-2-carboxamide

5-bromo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]thiophene-2-carboxamide (0.31g;0.76mmol) was stirred with 4-pyridylboronic acid (0.093g;0.76mmol), tetrakis(triphenylphosphine)palladium(0) (0.045g;5 mol%) and anhydrous sodium carbonate (0.089g;0.84mmol) in water (14ml) and DME (14ml) and the whole heated at reflux under Ar (18 hours). The reaction mixture was poured into 10% Na_2CO_3(aq) (30ml) and extracted into $CHCl_3$. The organic extracts were combined, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to a brown gum. The gum was purified by flash silica-gel chromatography and eluted with 4%MeOH/$CHCl_3$ to yield a yellow,semi-solid residue which was triturated with acetone/Et_2O. The solid that formed was collected by filtration and dried *in vacuo* to yield the title compound as a yellow solid (0.2g;65%), mp=191-194°C.

^{1}H NMR (250MHz, $CDCl_3$) δ : 8.65(d,2H), 7.90(s,1H), 7.60(d,1H), 7.55-7.45(m,3H), 7.30-7.20(m,2H), 6.80(d,1H), 3.90(s,3H), 3.25-3.05(m,4H), 2.70-2.55(m,4H), 2.40(s,3H)

Example 9

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-(4-pyridyl)pyridine-5-carboxamide

2-Bromo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]pyridine-5-carboxamide (0.125g;0.31mmol) was stirred with 4-pyridylboronic acid (0.038g;0.31mmol), tetrakis(triphenylphosphine)palladium(0) (0.024g) and anhydrous sodium carbonate

(0.036g;0.34mmol) in water (5ml) and DME (5ml) and the whole heated at reflux under Ar (18 hours). The reaction mixture was poured into 10% Na_2CO_3(aq) (20ml) and extracted into $CHCl_3$. The organic extracts were combined, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to a brown gum. The gum was purified by flash silica-gel chromatography and eluted with 5%MeOH/$CHCl_3$ to yield a orange/yellow gum(0.060g;48%).

^{1}H NMR (200MHz, $CDCl_3$) δ : 9.20(s,1H), 8.75(s,2H), 8.60(s,1H), 8.35(d,1H), 8.00-7.85(m,3H), 7.40(d,1H), 7.25(d,1H), 6.85(d,1H), 3.85(s,3H), 3.20-3.05(m,4H), 2.75-2.60(m,4H), 2.40(s,3H)

Example 10

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-(4-pyridyl)-3-methoxythiophene-4-carboxamide

2-Bromo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-3-methoxythiophene-4-carboxamide (0.20g;0.45mmol) was stirred with 4-pyridylboronic acid (0.056g;0.45mmol), tetrakis(triphenylphosphine)palladium(0) (0.024g) and anhydrous sodium carbonate (0.053g;0.50mmol) in water (5ml) and DME (5ml) and the whole heated at reflux under Ar (18 hours). The reaction mixture was poured into 10% Na_2CO_3(aq) (20ml) and extracted into $CHCl_3$. The organic extracts were combined, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to a brown gum. The gum was purified by flash silica-gel chromatography and eluted with 4%MeOH/$CHCl_3$ to yield a orange gum (0.088;44%).

^{1}H NMR (200MHz, $CDCl_3$) δ : 9.20(s,1H), 8.70(d,2H), 8.20(s,1H), 7.60(d,2H), 7.35-7.20(m,2H), 6.85(d,1H), 3.90(s,3H), 3.85(s,3H), 3.25-3.10(m,4H), 2.75-2.60(m,4H), 2.40(s,3H)

Example 11

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(2-pyridyl)thiophene-2-carboxamide

5-(pyrid-2-yl)thiophene-2-carboxylic acid (0.279g;1.36mmol) was heated at reflux in thionyl chloride (8ml) for 1 hour, cooled, evaporated *in vacuo* and the residue azeotroped with toluene. The orange residue was redissolved in CH_2Cl_2 (10ml) and treated with dry triethylamine (0.19ml;1.36mmol) and 4-methoxy-3-(4-methyl-1-piperazinyl)benzenamine

(0.3g;1.36mmol). The solution was stirred under Ar (18 hours), evaporated *in vacuo* and partitioned satd. K_2CO_3(aq) / EtOAc. The organic phases were combined, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to a brown gum. The gum was purified by flash silica-gel chromatography and eluted with 2%MeOH/$CHCl_3$ to yield the title compound as a orange gum (0.37g;67%), which was converted to the oxalate salt, mp=131°C(dec).

^{1}H NMR (250MHz, $CDCl_3$) (free base) δ : 8.55(d,1H), 8.45(s,1H), 7.80-7.60(m,3H), 7.55(d,1H), 7.40-7.30(m,1H), 7.25-7.15(m,2H), 6.80(d,1H), 3.85(s,3H), 3.20-3.00(m,4H), 2.70-2.50(m,4H), 2.35(s,3H)

Example 12

N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-3-nitro-4-pyrazolylbenzamide

As for Example 5 using 3-nitro-4-pyrazolylbenzoic acid (200mg, 0.86mmol), toluene (40ml), thionyl chloride (2ml), and DCM (40ml), triethylamine (2ml) and the amine (189mg, 0.85mmol).
The resulting oil was purified by column chromatography (silica, chloroform/methanol 5-30%) to afford the title compound as an oil (371mg, 100%) which was crystallised as an oxalate salt from methanol/chloroform.

1H NMR (D6-DMSO) 2.78 (3H, s), 3.73 (8H, bm, 4xCH2), 3.81 (3H, s), 6.65 (1H m), 7.01 (1H, d), 7.41 (1H, m), 7.50 (1H, d), 7.82 (1H, m), 8.00 (1H, d), 8.37 (1H, m), 8.46 (1H, m), 8.53 (1H, m), 10.41 (1H, bs, NH)..

Mass Spectrum M^+ found 436
$C_{22}H_{24}N_6O_4$ requires 436

Analysis Found C 54.32; H 4.92; N 15.73.
$C_{22}H_{24}N_6O_4.1.1C_2H_2O_4$ requires C 54.28; H 4.90; N 15.70.

Example 13

N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(4-ethoxycarbonylpiperazin-1-yl)benzamide

Ethyl 4-(4-ethoxycarbonylpiperazin-1-yl)benzoate (0.5g, 1.6mmol), conc.HCl (10ml) and 5N HCl (20ml) were heated at reflux for 45min, evaporated to dryness and dried in vacuo. The white solid was suspended in thionyl chloride (2ml) and dry toluene (40ml) and heated at reflux for 1h. The brown solution was evaporated to dryness under reduced pressure and dissolved in DCM (40ml), triethylamine (3ml) and N-4-methoxy-3-(4-methyl-1-piperazinyl)phenylamine(360mg,1.6mmol) added. The solution was stirred for 30min, partitioned between chloroform and saturated aqueous potassium carbonate solution, the organic solutions dried (sodium sulphate) and evaporated to dryness under reduced pressure. The solid was purified by flash column chromatography using silica and eluting with chloroform/MeOH (4-10%) to afford the title compound as a solid (295mg, 38%).

1H NMR ($CDCl_3$) 1.31 (3H, t), 2.41 (3H, s), 2.63 (4H, bs), 3.15 (4H, bs), 3.31 (4H, bm), 3.66 (4H, bm), 3.88 (3H, s), 4.19 (2H, q), 6.85 (1H, d), 6.95 (2H, d), 7.30 (1H, s), 7.65 (1H, s), 7.80 (2H, d).

Mass Spectrum M^+ found 481
$C_{26}H_{35}N_5O_4$ requires 481

Example 14
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-fluorobenzamide

4-Fluorobenzoyl chloride (0.23ml, 1.95mmol) with 4-methoxy-3-(4-methyl-1-piperazinyl)phenylamine (400mg, 1.95mmol) in dry dichloromethane (40ml) and triethylamine (1ml) was stirred for 1h. The solution was partitioned between dichloromethane (40ml) and saturated aqueous potassium carbonate (40ml), the organic solution dried (sodium sulphate) and evaporated to dryness under reduced pressure to afford an oil, which was purified by column chromatography (silica, chloroform,/methanol 5%) to afford the title compound (595mg, 89%) which was crystallised from methanol/diethyl ether as the oxalate salt.

1H nmr (d6-DMSO) δ 2.77 (3H, s), 3.25 (8H, bs), 3.81 (3H, s), 6.99 1H, d), 7.38 (3H, m), 7.48 (1H, d), 8.04 (2H, d), 10.12 (1H, s, NH).

Mass spectrum M^+ 343 $C_{19}H_{22}N_3O_2$ requires 343.

Elemental analysis C 56.72, H 5.58, N 9.25%
$C_{19}H_{22}N_3O_2.1.2(C_2H_2O_4)$ requires C 56.94, H 5.41, N 9.31%

Example 15

N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-chlorobenzamide

4-Chlorobenzoic acid (350mg, 2.23mmol) was heated at reflux with thionyl chloride (3ml) and toluene (40ml) for 2h, and then evaporated to dryness under reduced pressure. 4-Methoxy-3-(4-methyl-1-piperazinyl)phenylamine (494mg, 2.23mmol) in dry dichloromethane (40ml) was added with triethylamine (2ml) and the mixture stirred for 1h. The solution was partitioned between dichloromethane (40ml) and saturated aqueous potassium carbonate (40ml), the organic solution dried (sodium sulphate) and evaporated to dryness under reduced pressure to afford an oil, which was purified by column chromatography (silica, chloroform./methanol 5%) to afford the title compound (774mg, 97%) which was crystallised from methanol/diethyl ether as the oxalate salt.

1H nmr (free base) ($CDCl_3$) δ 2.38 (3H, s), 2.64 (4H, bs), 3.14 (4H, bs), 3.89 (3H, s), 6.85 (1H, d), 7.20 (1H, s), 7.48 (1H, d), 7.68 (1H, s), 7.81 (1H, d).

Example 16

N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-iodobenzamide

4-Iodobenzoic acid (350mg, 1.60mmol) was heated at reflux with thionyl chloride (3ml) and toluene (40ml) for 2h, and then evaporated to dryness under reduced pressure. 4-Methoxy-3-(4-methyl-1-piperazinyl)phenylamine (350mg, 1.60mmol) in dry dichloromethane (40ml) was added with triethylamine (2ml) and the mixture stirred for 1h. The solution was partitioned between dichloromethane (40ml) and saturated aqueous potassium carbonate (40ml), the organic solution dried (sodium sulphate) and evaporated to dryness under reduced pressure to afford an oil, which was purified by column chromatography (silica, chloroform./methanol 5%) to afford the title compound (649mg, 90%) which was crystallised from methanol/diethyl ether as the oxalate salt.

1H nmr (free base) ($CDCl_3$) δ 2.38 (3H, s), 2.68 (4H, bs), 3.19 (4H, bs), 3.89 (3H, s), 6.85 (1H, d), 7.20 (1H, s), 7.60 (1H, d), 7.68 (1H, s), 7.82 (1H, d).

Example 17

N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-cyclohexylbenzamide

4-Cyclohexylbenzoic acid (300mg, 1.5mmol) was heated at reflux with thionyl chloride (2ml) and toluene (40ml) for 2h, and then evaporated to dryness under reduced pressure. 4-Methoxy-3-(4-methyl-1-piperazinyl)phenylamine (325mg, 1.5mmol) in dry dichloromethane (40ml) was added with triethylamine (2ml) and the mixture stirred for 1h. The solution was partitioned between dichloromethane (40ml) and saturated aqueous potassium carbonate (40ml), the organic solution dried (sodium sulphate) and evaporated to dryness under reduced pressure to afford an oil, which was purified by flash column chromatography (silica, chloroform,/methanol 5%) to afford the title compound (561mg, 92%) which was crystallised from methanol/diethyl ether as the oxalate salt m.p.117-119°C.

1H nmr (d6-DMSO) δ 1.41 (5H, m), 1.78 (5H, m), 2.58 (1H, m), 2.78 (3H, s, NMe), 3.25 (8H, m), 3.78 (3H, s, OMe), 6.94 (1H, d), 7.34 (2H, d), 7.45 (2H, m), 7.85 (2H, d), 10.00 (1H, s, NH).

Mass spectrum M^+ 407 $C_{25}H_{33}N_3O_2$ requires 407.

Elemental analysis C 64.33, H 6.88, N 8.30%
$C_{19}H_{22}N_3O_2.1.2(C_2H_2O_4)$ requires C 64.03, H 7.11, N 8.30%

Example 18

N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-tert-butylbenzamide

4-^{t}Butylbenzoic acid (300mg, 1.7mmol) was heated at reflux with thionyl chloride (2ml) and toluene (40ml) for 2h, and then evaporated to dryness under reduced pressure. 4-Methoxy-3-(4-methyl-1-piperazinyl)phenylamine (370mg, 1.6mmol) in dry dichloromethane (40ml) was added with triethylamine (2ml) and the mixture stirred for 1h. The solution was partitioned between dichloromethane (40ml) and saturated aqueous potassium carbonate (40ml), the organic solution dried (sodium sulphate) and evaporated to dryness under reduced pressure to afford an oil, which was purified by flash column chromatography (silica, chloroform,/methanol 5%) to afford the title compound (720mg, 100%) which was crystallised from methanol/diethyl ether as the oxalate salt m.p.220-222°C.

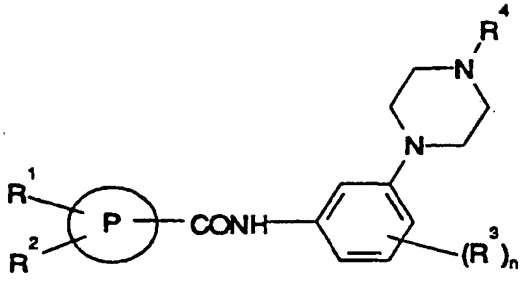
1H nmr (d6-DMSO) δ 1.35 (9H, s), 2.80 (3H, s), 3.23 (8H, bm), 3.80 (3H, s), 6.96 (1H, d), 7.49 (5H, m), 7.89 (2H, d), 10.04 (1H, s, NH).

Mass spectrum M^+ 381 $C_{23}H_{31}N_3O_2$ requires 381.

Elemental analysis C 63.15, H 6.89, N 8.91%
$C_{23}H_{31}N_3O_2.1.1(C_2H_2O_4)$ requires C 63.00, H 6.92, N 8.75%

CLAIMS:

1. A compound of formula (I) or a salt thereof:



(I)

in which

P is a phenyl or a 5 or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, nitrogen or sulphur;

R^1 is halogen, C_{1-6}alkyl, C_{1-6}cycloalkyl, optionally substituted phenyl or an optionally substituted 5-7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, trifluoromethyl or cyano;

R^3 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

R^4 is hydrogen or C_{1-6}alkyl; and

n is 1 or 2,

- provided that when P is phenyl R^1 is not pyridyl or phenyl.

2. A compound according to claim 1 in which P is phenyl, thienyl, furyl or pyridyl.

3. A compound according to claim 2 in which R^1 is halogen, butyl, cyclohexyl, pyridyl, pyrazolyl, triazolyl, imidazolyl, morpholinyl, piperazinyl or thienyl.

4. A compound according to claim 2 or 3 in which R^2 is hydrogen, C_{1-6}alkoxy, C_{1-6}alkyl, or nitro

5. A compound according to any one of claims 1 to 4 in which R^3 is C_{1-6}alkoxy.

6. A compound according to any one of claims 1 to 5 in which R^4 is C_{1-6}alkyl.

7. A compound according to claim 1 which is:

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(4-pyridyl)furan-2-carboxamide,

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(4-pyridyl)furan-3-carboxamide,

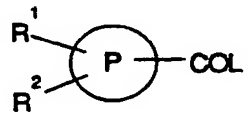
N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(4-pyridyl)thiophene-2-carboxamide,

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-(4-pyridyl)pyridine-5-carboxamide,

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-(4-pyridyl)-3-methoxythiophene-4-carboxamide,
N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(2-pyridyl)thiophene-2-carboxamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(1,2,4-triazol-1-yl) benzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(imidazol-1-yl) benzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(morpholin-1-yl) benzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(3-thiophenyl)-3-methylbenzamide,
N-(4-methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(1,2,4-triazol-1-yl)-3-nitrobenzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-3-nitro-4-pyrazolylbenzamide, or
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(4-ethoxycarbonylpiperazin-1-yl)benzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-fluorobenzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-chlorobenzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-iodobenzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-cyclohexylbenzamide,
N-(4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-tert-butylbenzamide,
or pharmaceutically acceptable salts thereof.

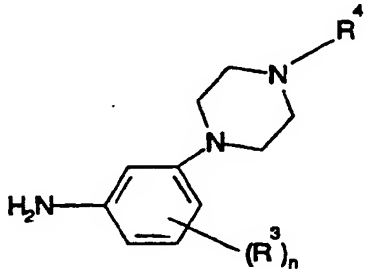
8. A process for the preparation of a compound of formula (I) which comprises

(a) reaction of a compound of formula (II):



(II)

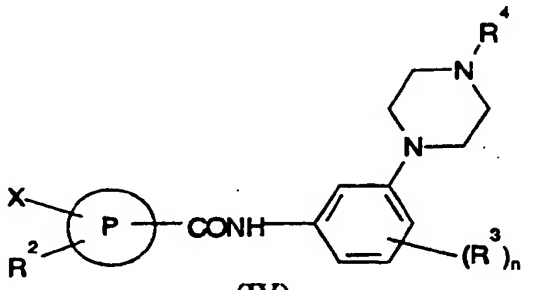
in which R^1, R^2 and P are as defined in formula (I) and L is a leaving group, with a compound of formula (III):



(III)

in which R^3, R^4 and n are as defined in formula (I);

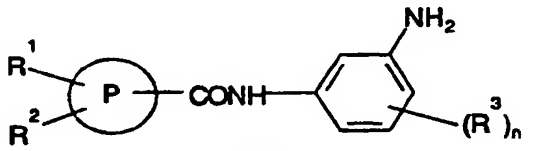
(b) for compounds of formula (I) in which R^1 is a phenyl or heterocyclic ring reaction of a compound of formula (IV):



(IV)

in which R^2, R^3, R^4, P and n are as defined in formula (I) and X is a leaving group with a nucleophile R^1 where R^1 is as defined in formula (I); or

(c) reaction of a compound of formula (V):



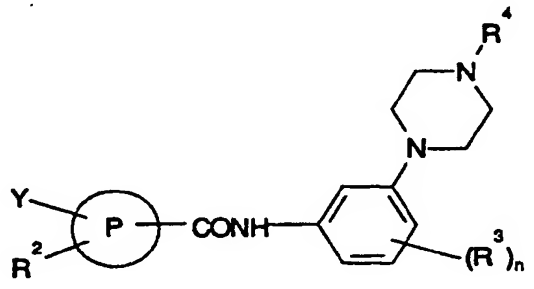
(V)

in which R^1, R^2, R^3, P and n are as defined in formula (I) with a compound of formula (VI):

$$R^4N(CH_2CH_2Hal)_2 \qquad (VI)$$

in which R^4 is as defined in formula (I) and Hal is halogen, or

(d) reaction of a compound of formula (VII):



(VII)

in which R^2, R^3, R^4, P and n are as defined in formula (I) and Y is halogen or a group

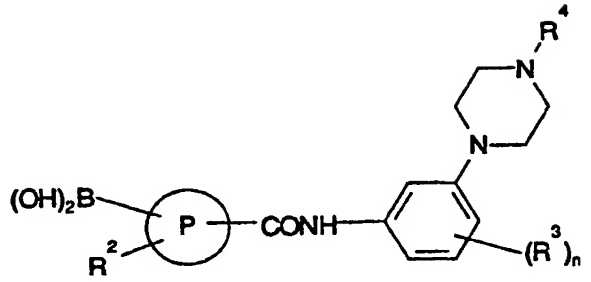
$-OSO_2CF_3$ with a compound of formula (VIII):

$$R^1B(OH)_2$$

(VIII)

in which R^1 is as defined in formula (I), or

(e) reaction of a compound of formula (IX):



(IX)

in which R^2, R^3, R^4, P and n are as defined in formula (I) with a compound of formula (X):

$$R^1Y$$

(X)

in which R^1 is as defined in formula (I) and Y is as defined in formula (VII),

and optionally thereafter:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

9. A compound according to any one of claims 1 to 7 for use in therapy.

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 in association with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 94/02492

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/14 C07D333/24 C07D405/04 C07D307/68 C07D409/04
C07D213/80 C07D295/20 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 533 266 (GLAXO GROUP LIMITED) 24 March 1993 cited in the application *Page 36-42: claims* ---	1-10
A	EP,A,0 533 267 (GLAXO GROUP LIMITED) 24 March 1993 cited in the application *Page 31-35: claims* ---	1-10
A	EP,A,0 533 268 (GLAXO GROUP LIMITED) 24 March 1993 cited in the application *Page 33-39: claims* --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 1994	27. 10. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Luyten, H

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	JOURNAL OF MEDICINAL CHEMISTRY, vol.37, no.15, 22 July 1994 pages 2253 - 2257 JOHN W. CLITHEROW ET AL *Complete article*	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/EP 94/02492

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0533266	24-03-93	AU-A-	2452992	25-03-93
		CA-A-	2078506	19-03-93
		JP-A-	6107649	19-04-94
EP-A-0533267	24-03-93	AU-A-	2452892	25-03-93
		AU-A-	2568792	27-04-93
		CA-A-	2078507	19-03-93
		CN-A-	1073430	23-06-93
		WO-A-	9306084	01-04-93
		FI-A-	941261	17-03-94
		JP-A-	6107637	19-04-94
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		AU-A-	2453092	25-03-93
		CA-A-	2078505	19-03-93
		HU-A-	65608	28-07-94
		JP-A-	6116251	26-04-94
		US-A-	5340810	23-08-94
		CN-A-	1076195	15-09-93